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del carcinoma prostatico ad alto rischio

Hypofractionation in high risk prostate cancer: Controversies

Programma Prostata, Direzione Scientifica
Istituto Nazionale Tumori, Milano

Fondazione IRCCS Istituto Nazionale dei Tumori

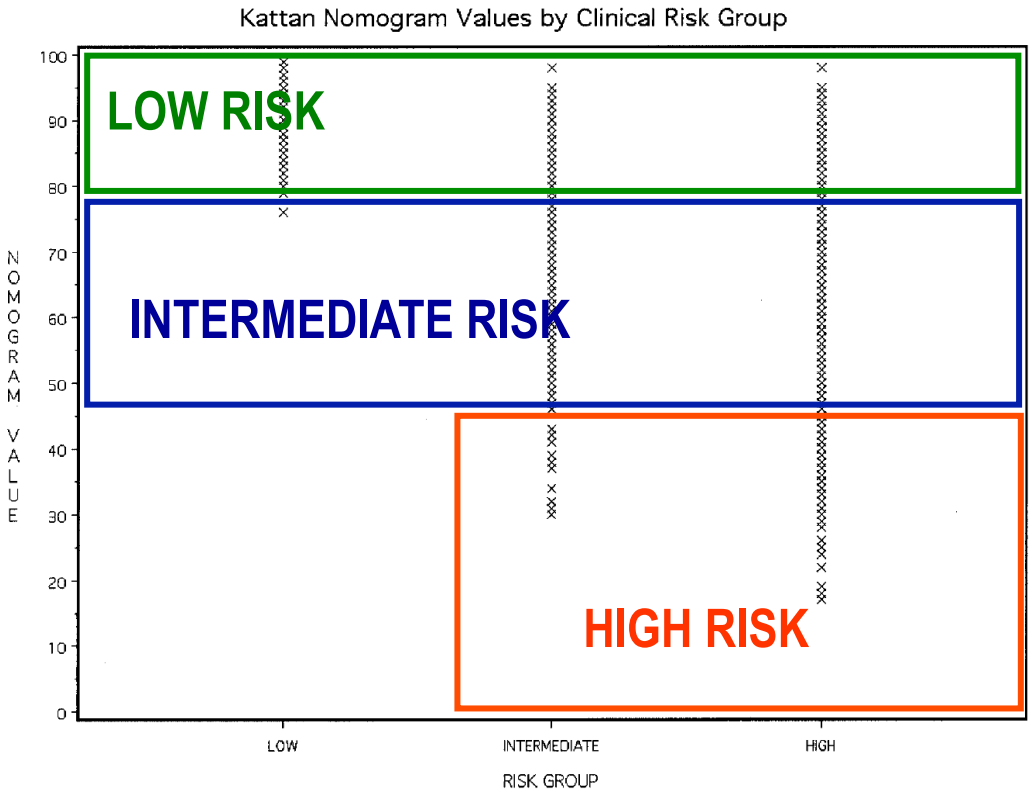
PROGRAMMAPROSTATA

Ouline: Critical Issues

1. High risk class: clinical heterogeneity
2. Definition of hypofractionation
3. Evaluation of treatment outcome
4. Hypoxic cores in high risk prostate cancer
5. α/β value(s)
6. Late toxicity concern
7. FCCC ® Trial: HIMRT vs CIMRT

Critical Issue 1: High risk class: clinical heterogeneity

High risk class includes a highly heterogeneous group of cancers. This introduces a potential confounding variable in the evaluation of clinical results. (Gerber et al, Eu Urol, 2010; Tendulkar et al, IJROBP, 2011)



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ABILITY OF 2 PRETREATMENT RISK ASSESSMENT METHODS TO PREDICT PROSTATE CANCER RECURRENCE AFTER RADICAL PROSTATECTOMY: DATA FROM CaPSURE

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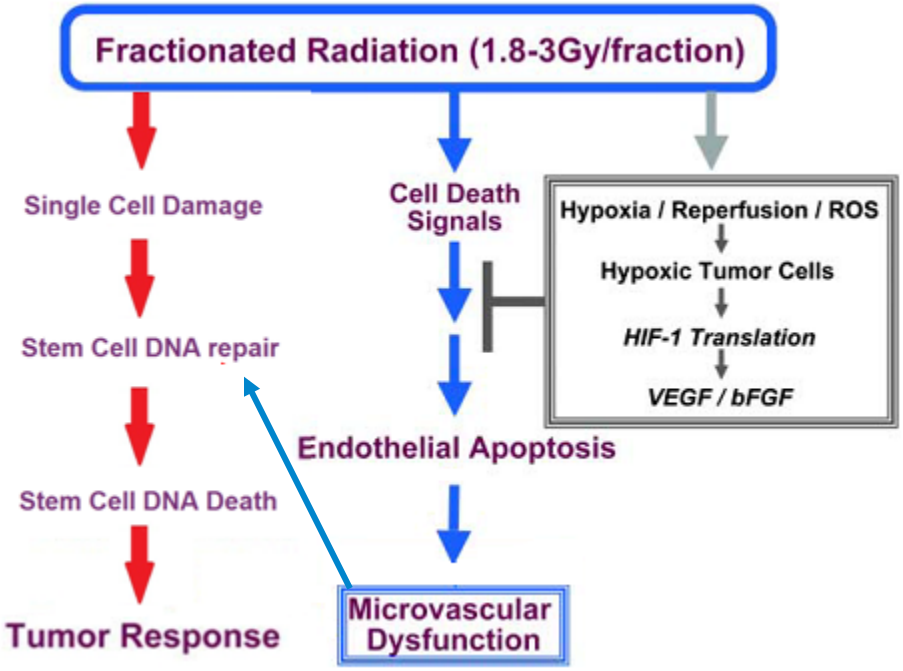
Critical Issue 2: Definition of hypofractionation

We should clearly distinguish between:

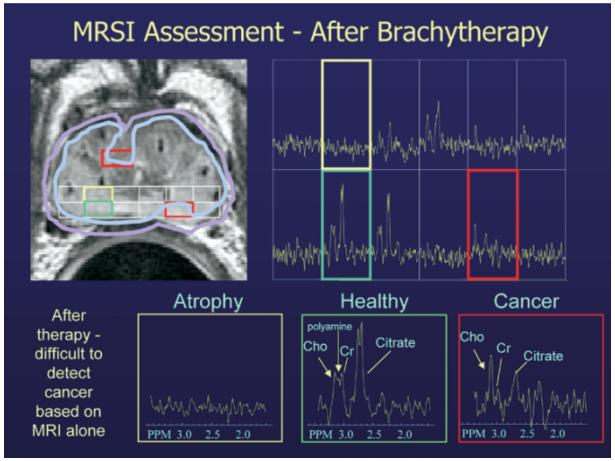
1. *hypofractionation schemes involving ≈2.2-3 Gy/fr, where clonogenic cell killing is the dominant effect of radiation, which is well described by the LQ model*



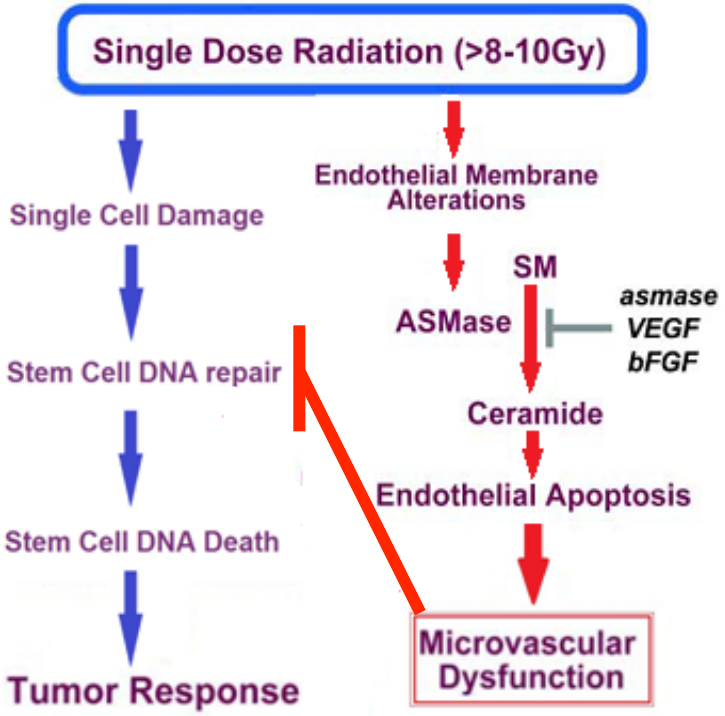
Fuks and Kolesnick, Cancer Cell 2005

Critical Issue 2: Definition of hypofractionation

2. *and regimens involving very high doses/fr (>8 Gy), where stromal damage is the dominant effect, α/β ratio probably plays a minor role (if any) and tissue injury can be described as a form of radio-ablation involving either a clonogenic cell killing and a* ***preminent vascular default***



Pickett et al, IJROBP 2006



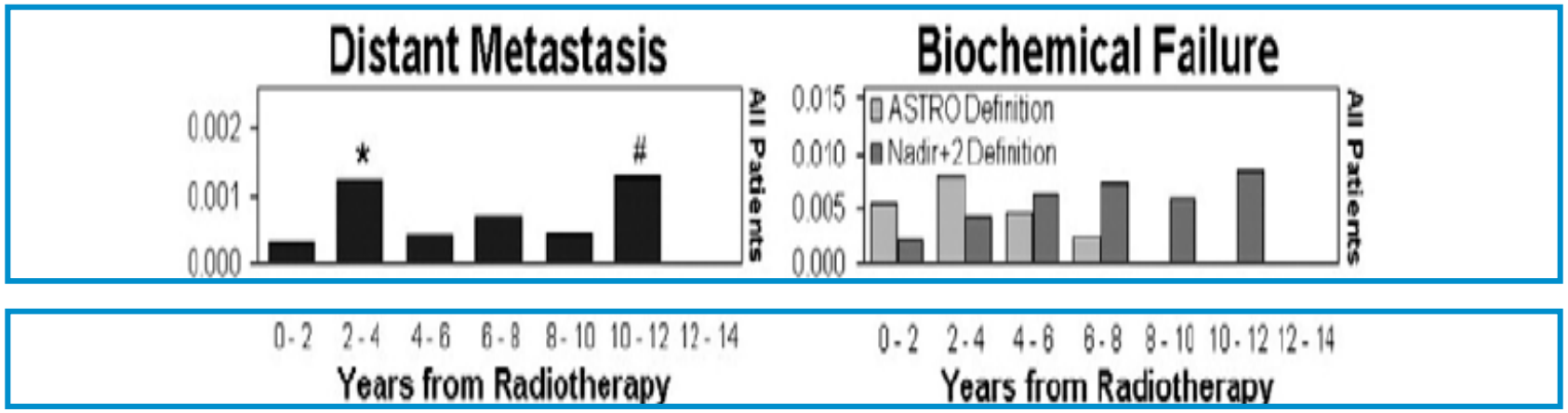
Fuks and Kolesnick, Cancer Cell 2005
McBride et al. ASTRO 2011
Kolesnick, ASTRO 2011

Critical Issue 3: Evaluation of treatment outcome

Dealing with radiotherapy efficacy (and evaluating α/β ratio), histologically confirmed **local control/failure** should be the **optimal end point**.

Unfortunately, most clinical **trials do not give such information**, biochemical failure being largely used as a surrogate for local control/failure.

The impossibility of distinguishing between distant and local failure introduces a significant uncertainty in the analytic process and consequently in the α/β estimates.



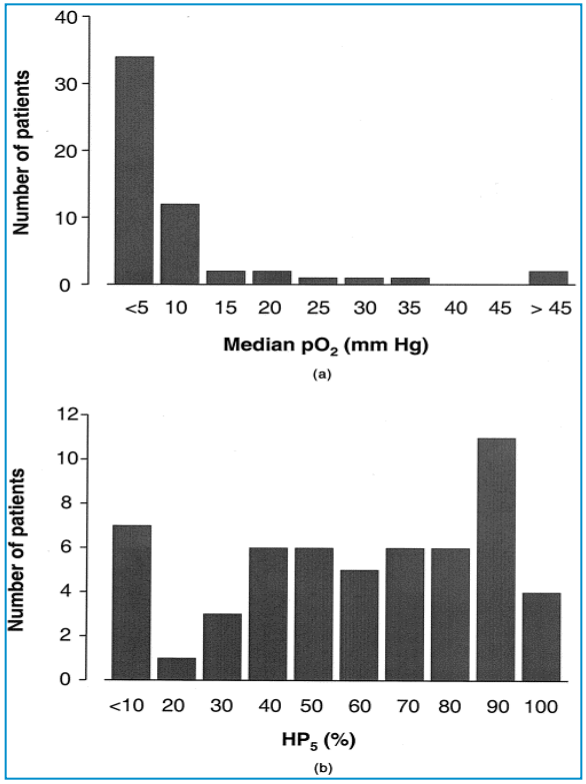
Morgan, ASTRO 2006, IJROBP, 66(S3)

Critical Issue 4: Hypoxic cores in HR prostate cancer

1. Direct **evidence** that **hypoxia does exist in prostate cancer** and that it **impacts** on **radiotherapy failures** as shown by pre-clinical and clinical investigations.

Evidences of the presence of hypoxia in PCa:

- Eppendorf (Movsas et al, 1999; 2002; Parker et al, 2004, Turaka et al., 2011, Bristow, ASTRO 2011)
- PET (Milosevic et al, 2004)
- Neutron vs photon experience (Forman et al, 2004)
- Pimonidazole (Carnell, 2006)
- HIF dependent biomarkers (Boddy, 2005; Vergas and Parker, 2008)
- AD effect (Milosevic et al, 2006)
- MR BOLD imaging (Hoskin, 2007)



Critical Issue 4: Hypoxic cores in HR prostate cancer

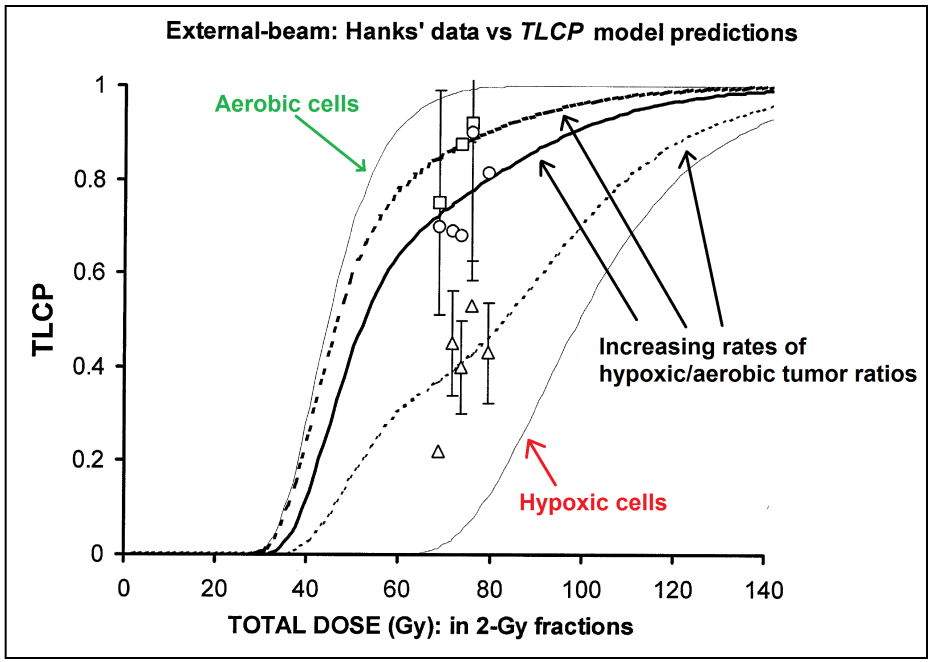
2. Recently shown that **hypoxic regions increase from low to high risk disease** (Bristow, ASTRO, 2011).

3. Consequently, **a larger α/β value for high risk patients** should be expected, α/β value for hypoxic clonogens being about 6 times higher than for well-oxygenated ones.

PSA levels of ≤10 ng/ml (□□)

PSA levels of 10–20 ng/ml (○○)

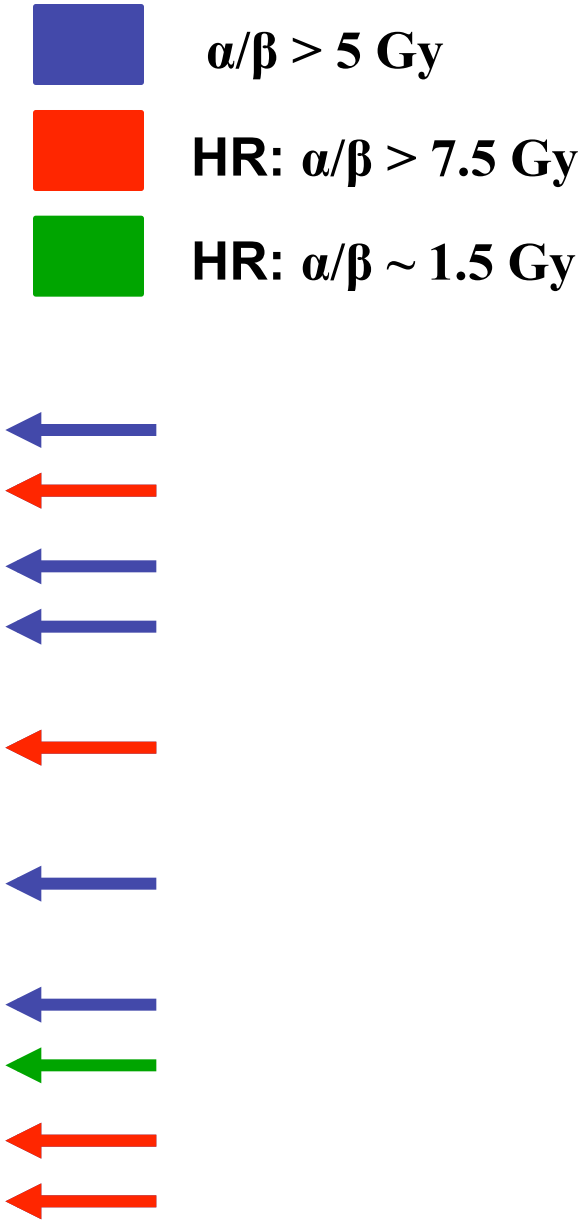
PSA levels of ≥20 ng/ml (△△)



Nahum et al. IJROBP 2003

Critical Issue 5: α/β values

Brenner and Hall (1999)	**1.5** (0.8-2.2)
King and Mayo (2000)	**4.96**
Brenner and Hall (2000)	**2.1**
King and Fowler (2001)	**1.8-2.0**
Fowler et al. (2001)	**1.49** (1.25-1.76)
Kal et al. (2003)	**3.1-3.9**
Wang et al. (2003)	**3.1** (+/- 0.5)
Nahum et al. (2003)	**8.3** (oxygenated cells)
Nahum et al. (2003)	**15.5** (hypoxic cells)
Lindsay et al. (2003)	**1.1-12.3** (BCT)
Valdagni et al. (2005)	**8.3** (0.7-16.0)
Lukka et al. (2005)	**1.12** (-3.3-5.6)
Williams et al. (2006)	**2.6-3.7 (6.5 IR- 7.6 HR)**
Mirabell et al. (2009)	**1.3-1.8**
Pollack et al. (2009)	**6.5 or higher**
Proust-Lima et al. (2010)	**1.55**
Shaffer et al. (2010)	**5.2 - >30**
Arcangeli et al. (2010) ®	**1.4 HR**
Valdagni et al. (2011)	**3.2 LIR – 9 HR**
Pollack et al. (2011) ®	**5.3 (IR – HR)**



Critical Issue 6: Late toxicity concern

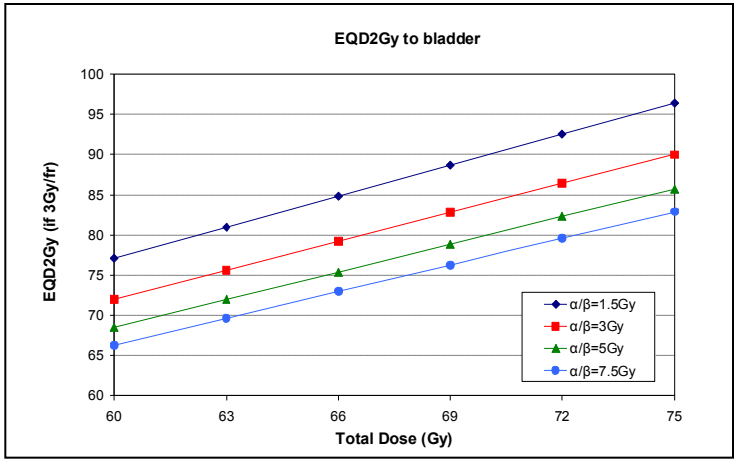
1. As clearly stated by **Quantec** (IJROBP, 2010), **definitive information on α/β of organs at risk** (rectum, bladder, penile bulb?, bowel loops) are **still lacking** and consequently, no reliable **information of equivalent doses for late toxicity** are **available**

2. With hypofractionation, an increase in acute toxicity has to be expected and it might be reasonable to note an increase in late toxicity due to a **sequential effect** between acute and late injury (Heemsbergen et al, IJROBP 2006, Fellin et al, IJROBP 2008, Valdagni et al., IJROBP, 2011)

Critical Issue 6: Late toxicity concern

3. Consequently, dose-volume contraints for late toxicity should be carefully considered, e.g.

- **late faecal incontinence** is related to dose bath at ≈ 40Gy at 2Gy/fr and this translates into a dose bath constraint of ≈ 30Gy at 2.5-3 Gy/fr (with α/β=1.5~5Gy)
- **GU toxicity** seems to be essentially related to the dose to **the bladder neck**, which is the **prescribed dose** (≈ 80 Gy equivalent doses, with α/β=1.5~5Gy). So far, despite the sophistication in technology, no attempt to sculpt the dose around the bladder neck

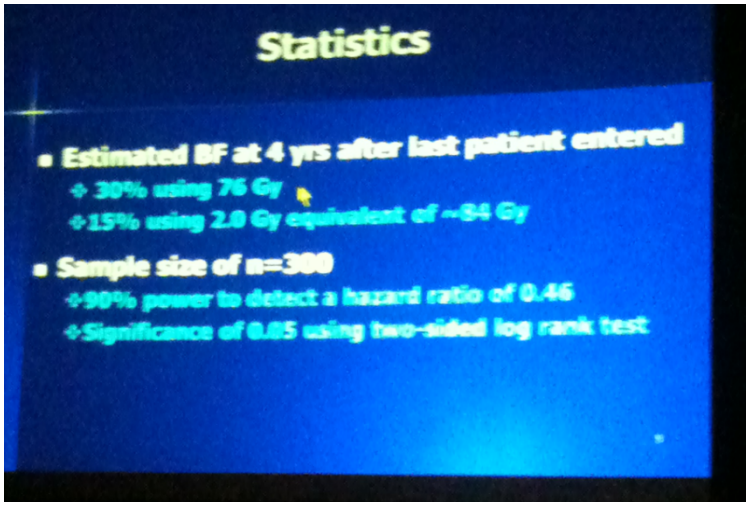


FCCC Hypofractionated Trial (Intermediate/High Risk)

Pollack et al, ASTRO, 2011

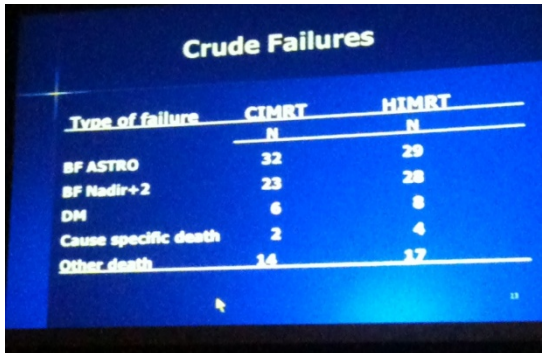
Estimated BF at 4 yrs after last patient entered:

- 30% using 76 Gy (CIMRT)
- 15% using 2.0 Gy equivalent of ~84 Gy
  (70.2 Gy - 2.7 Gy in 26 fr) (HIMRT)



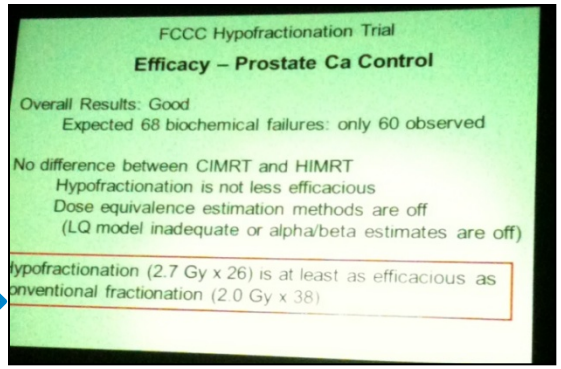
FCCC Hypofractionated Trial: Results

1. Hypofractionation (HIMRT): **more BF at 5yr** (28 vs 23, Phoenix def)



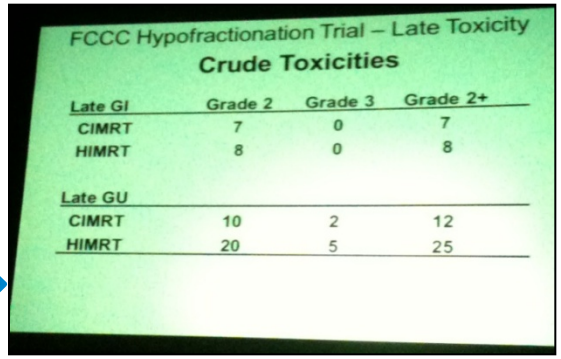
2. Failure and α/β : HIMRT **not superior** to CIMRT, suggesting **α/β ratio may be higher than 1.5** (IR+HR: 5.3 Gy)

"Dose equivalence estimation methods are off "*(Kupelian, ASTRO 2011)*



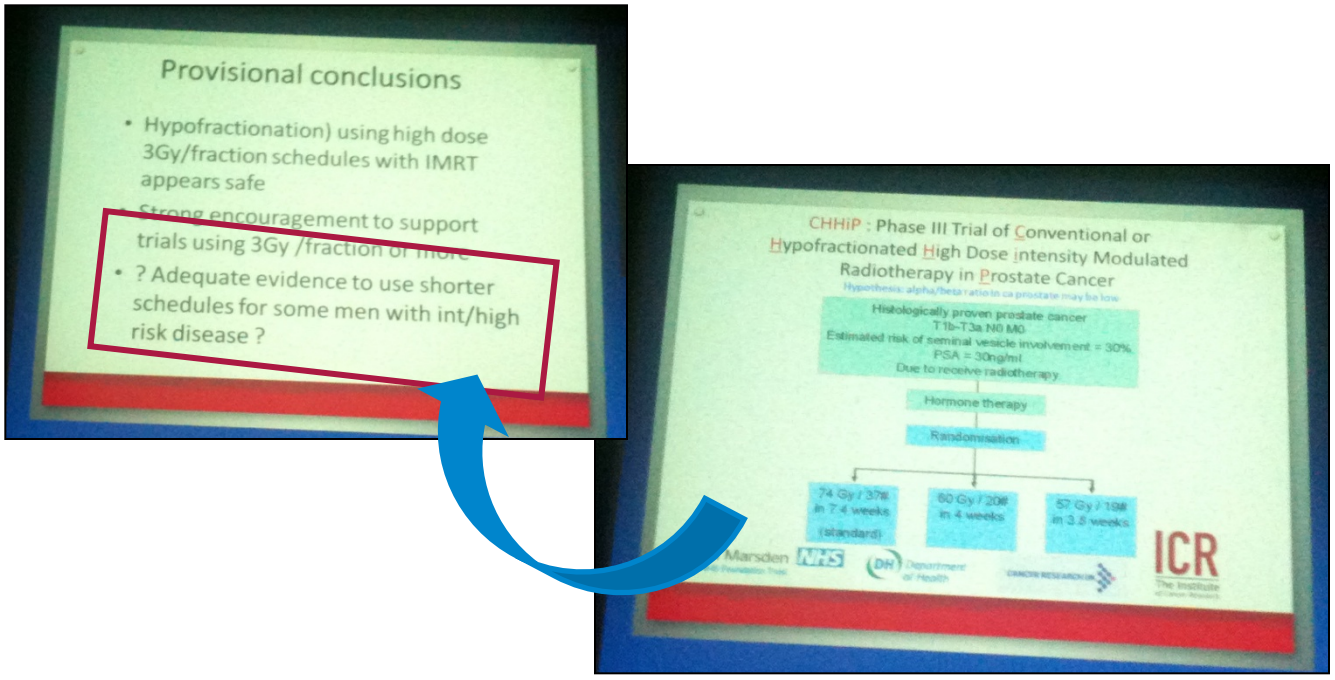
3. Late toxicity: **GU Toxicity** significantly **higher with HIMRT**

(Grade ≥2: 12% vs 25%, p<0.05)



Conclusions

1. *Difficult to state a conclusive point about the use of moderate hypofractionation in high risk prostate cancer patients:* ***FCCC ® trial (IR & HR disease) failed to prove hypo superiority over conventional fractionation and is failing to prove α/β ratio is 1.5 Gy in high risk disease***



D. Dearnely, EMUC, Nov 4 2011

Conclusions

2. Particular attention should be paid to dose-volume constraints for OaR, and IGRT should be recommended

3. GU tox appears to be, and probably will be, a real concern

4. Lacking EB on low α/β in high (and intermediate) risk patients, a moderate hypofractionation (e.g. 74.2 Gy, 2.65 Gy/fr, equivalent to 88Gy if α/β=1.5 Gy and to 78.2 Gy if α/β=10Gy) seems to have a good rationale: useful in reducing treatment time (28 fractions) and sufficiently safe

5. Radioablative doses (>8 Gy/fraction) are opening a new radiobiological era but no data on clinical efficacy (and toxicity) are available in high risk patients